Non-alcoholic fatty liver disease: Choosing the right path

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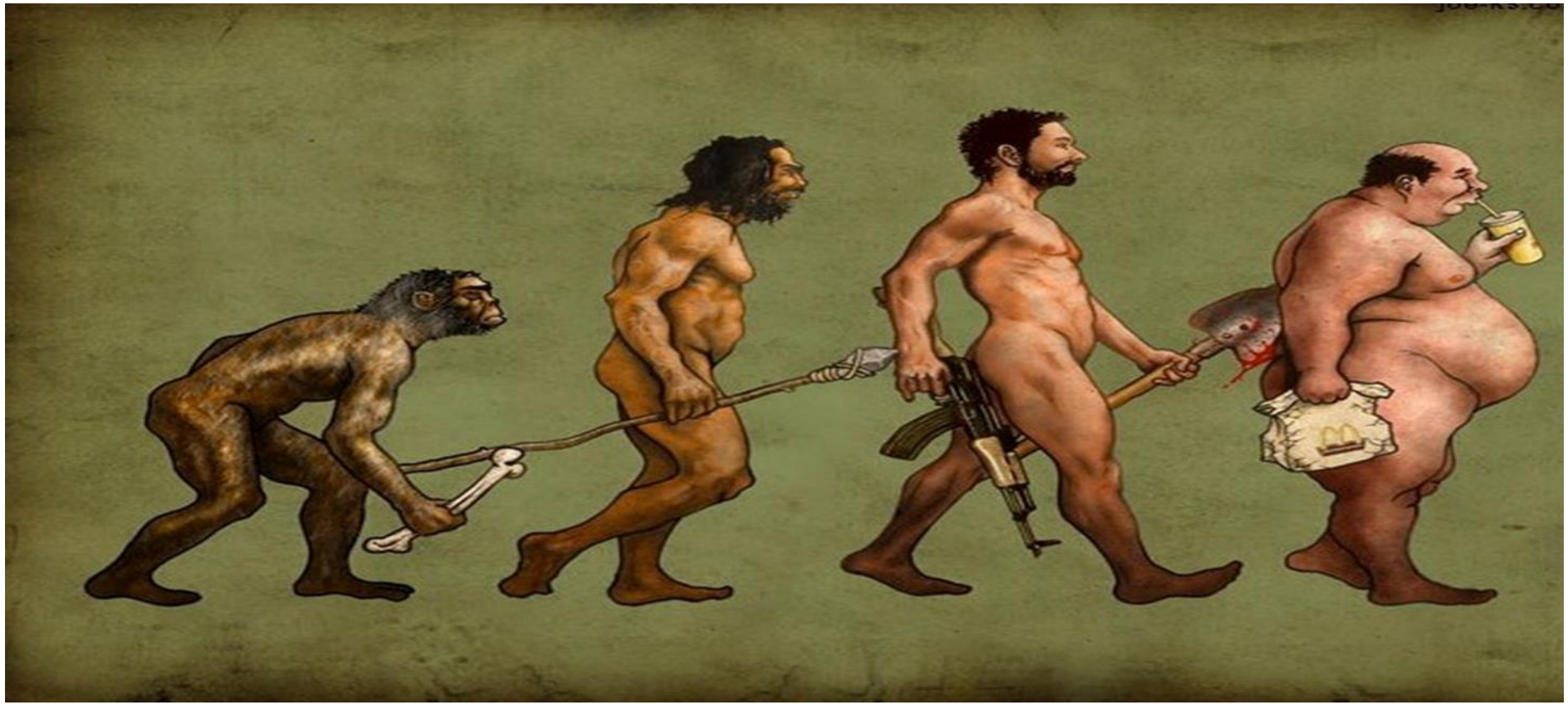
Discussion outline

1. Introduction
2. Diagnostic criteria of NAFLD
3. Prevalence and relationship among DM, obesity and fatty liver
4. NAFLD pathogenesis
5. Investigations of NAFLD
6. Treatment of NAFLD
7. Role of GLP 1 Analogue and PPAR agonist

Introduction-

We are in the era of NAFLD



Diagnostic criteria for NAFLD according to the various guidelines

Required criteria by EASL

- Steatosis in > 5% of hepatocytes either by Imaging or Histology
- No other causes of steatosis.
- Alcohol consumption:
  - Male <30 g /day, female<20 g/day

AASLD guideline

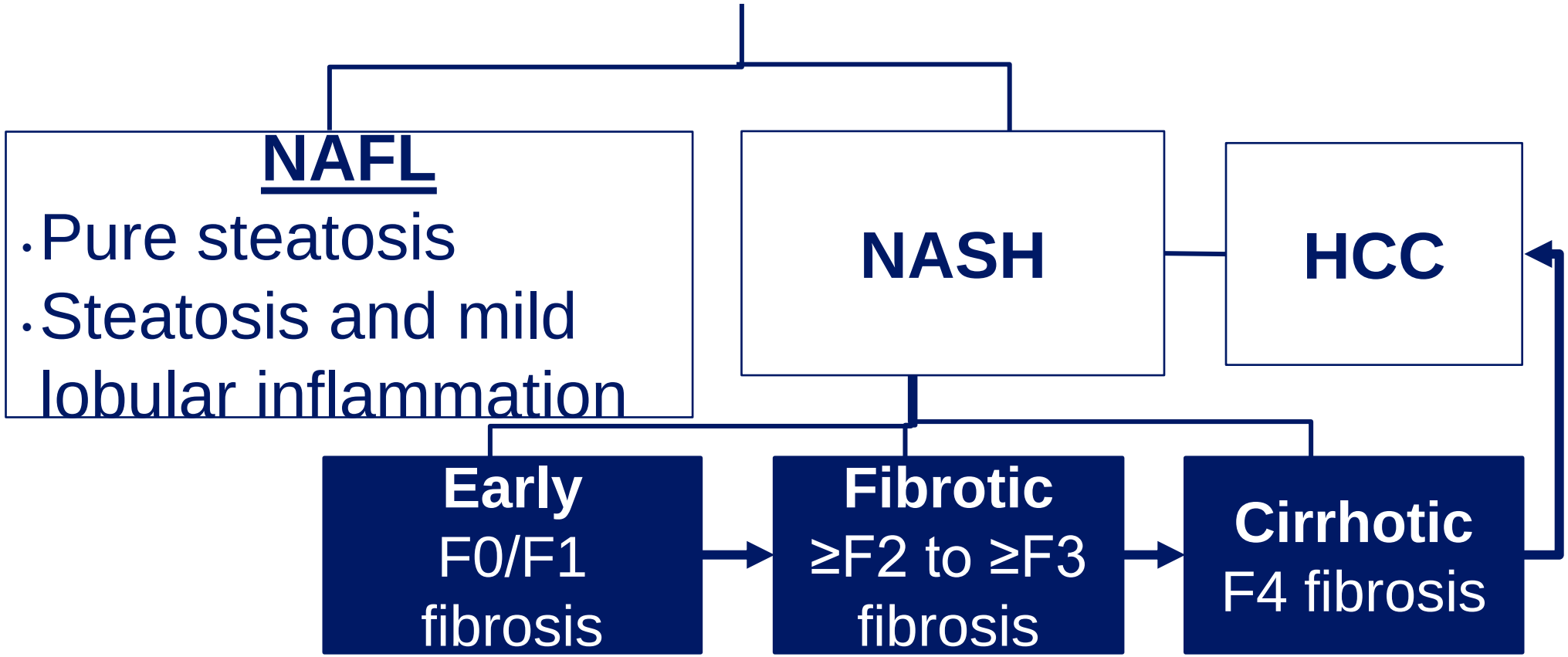
- Steatosis of hepatocytes either by Imaging or histology.
- No other causes of steatosis.
- No existing chronic liver disease
- No significant Alcohol consumption:

(male <294 g /week, female<196 g/week)

Definitions of NAFLD, NAFL and NASH

Definitive diagnosis of NASH requires a liver biopsy

NAFLD



*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Prevalence of fatty liver:

- The overall global prevalence of NAFLD by imaging is around 25.24% (1)
- **The highest prevalence-**
  - in Middle East-31.79%, & in Western hemisphere 20%-30% of the adult population (2)
- South America 30.45% & lowest prevalence rate is in Africa 13.48% (1)
- Prevalence of NAFLD in men is 2 times higher than in women.(3,4,5)

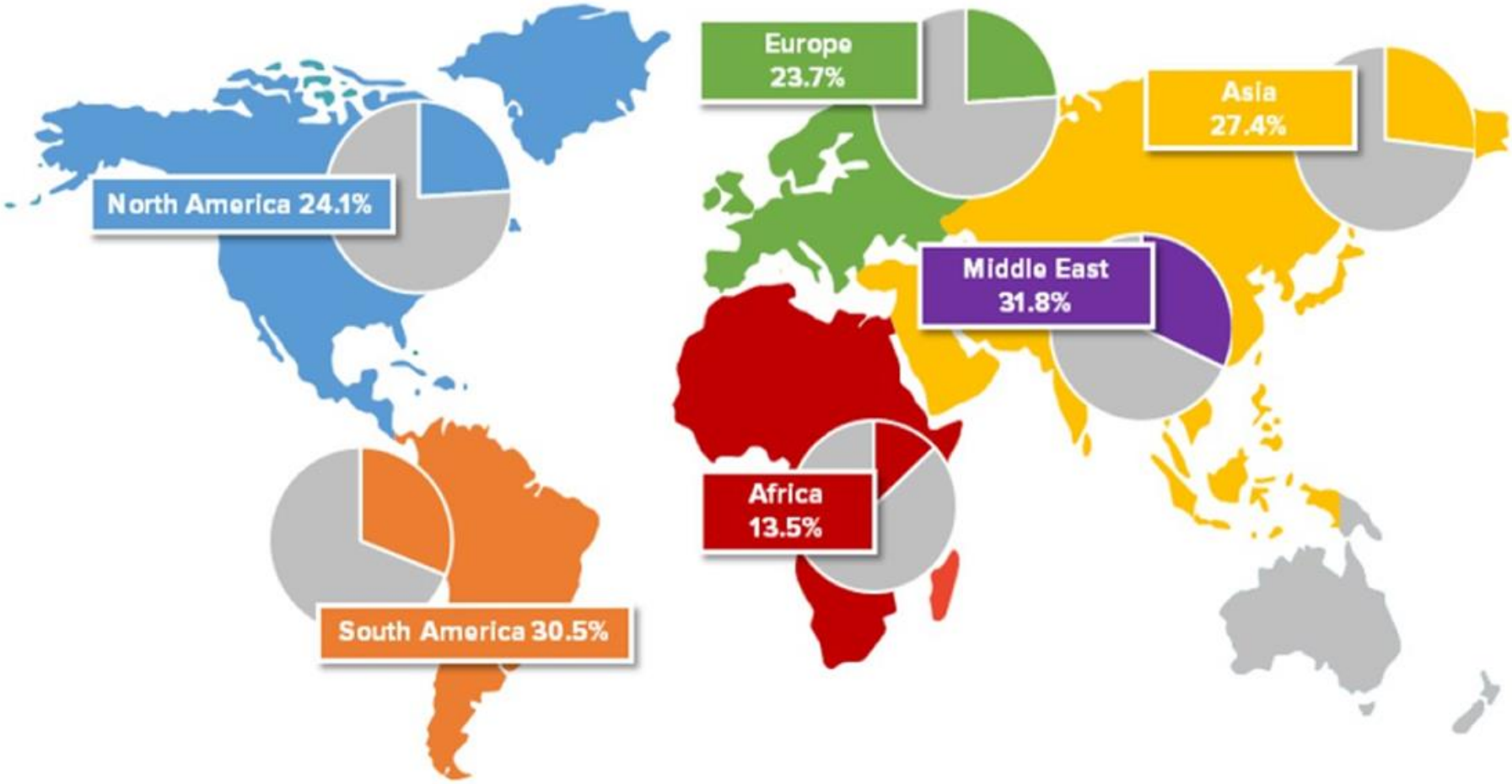
1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. HEPATOLOGY 2016;64:73-84.
2. [Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver. Clin Liver Dis. 2004;8:501–519.]
3. Fattahi MR, Niknam R, Safarpour A, Sepehrimanesh M, Lotfi M. The prevalence of metabolic syndrome in non-alcoholic fatty liver disease; a population-based study. Middle East J Dig Dis 2016;8:131-137.
4. Park KS, Lee YS, Park HW, Seo SH, Jang BG, Hwang JY, et al. Factors associated or related to with pathological severity of nonalcoholic fatty liver disease. Korean J Intern Med 2004; 19:19-26.
5. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int 2006;26:856-863.

NAFL NASH, HCC

- Approximately 10%-25% patients with NAFLD can progress to NASH.(1)
- **10%-15% patients with NASH develop HCC (2,3)**
- **NAFLD-third-most common cause of HCC in the United States.(4)**

1.(Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. HEPATOLOGY 2016;64:73-84.
2 Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Jarvinen H, Svegliati-Baroni G. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis. 2010;42:320–330.
3. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Cleve Clin J Med. 2008;75:721–728. (>95%) of patients with severe obesity undergoing bariatric surgery have NAFLD
4) Mohamad B, Shah V, Onyshchenko M, Elshamy M, Aucejo F, Lopez R, et al. Characterization of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) patients without cirrhosis. Hepatol Int 2016;10:632-639.

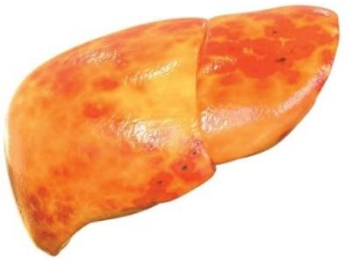
Global Prevalence of NAFLD



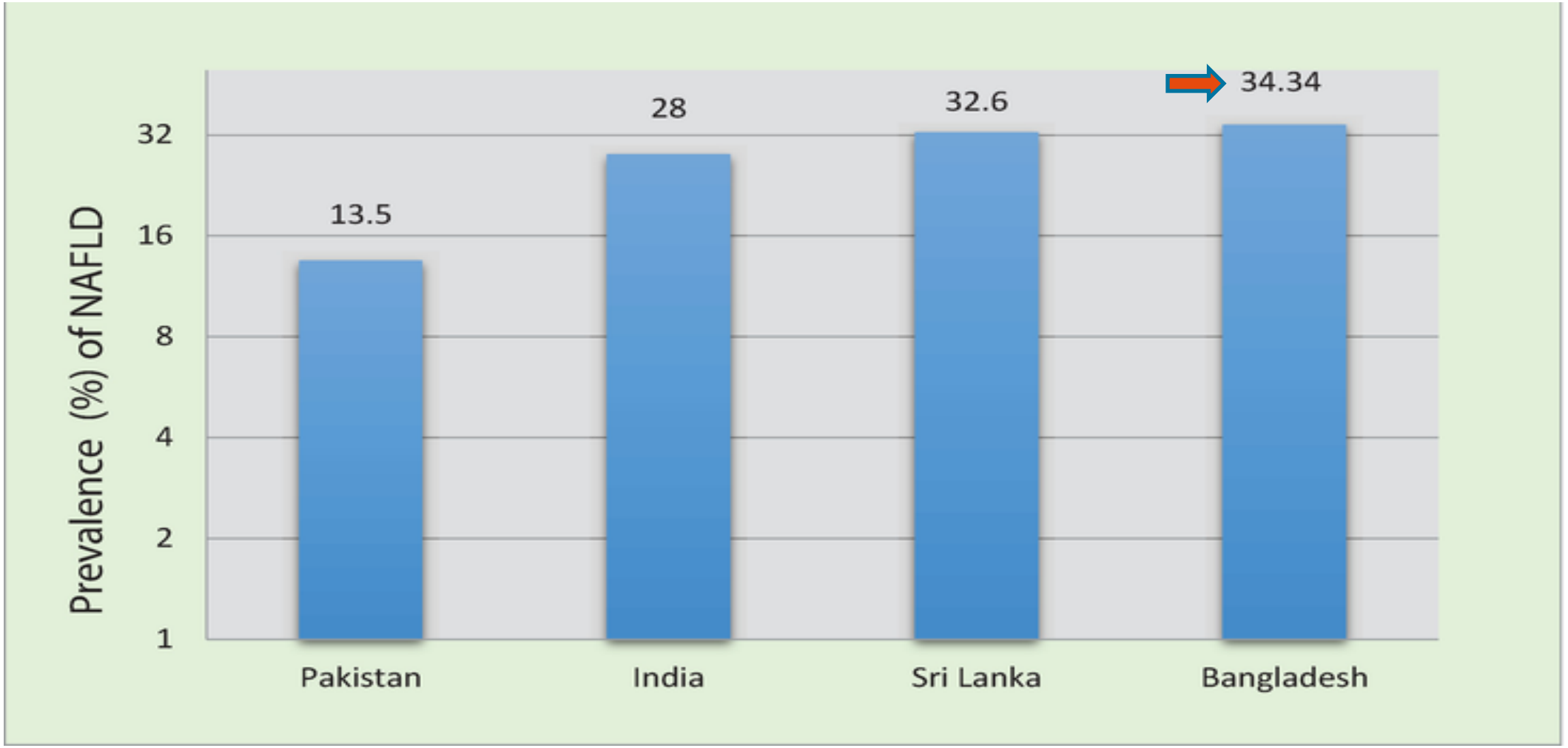
- **NAFLD** prevalence: **25%** of the general population
- **Prevalence is highest in the Middle East and South America**

NAFLD, nonalcoholic fatty liver disease.

Younossi ZM, et al. Hepatology 2016;64:73-84.



NAFLD: BANGLADESH



S Alam et al JGH Open: An open access journal of gastroenterology and hepatology (2018) 1–8

Metabolic syndrome (MS)

Defined by **Adult Treatment Panel III (ATP-III),**

MS is the presence of three or more of the following features:

1. Waist circumference >102 cm in men or >88 cm in women.
2. TG level ≥150 mg/dL
3. HDC-cholesterol level <40 mg/dL in men & <50 mg/dL in women.
4. A SBP ≥130 mmHg or DBP ≥85 mm Hg.
5. A fasting plasma glucose level ≥110 mg/dL.

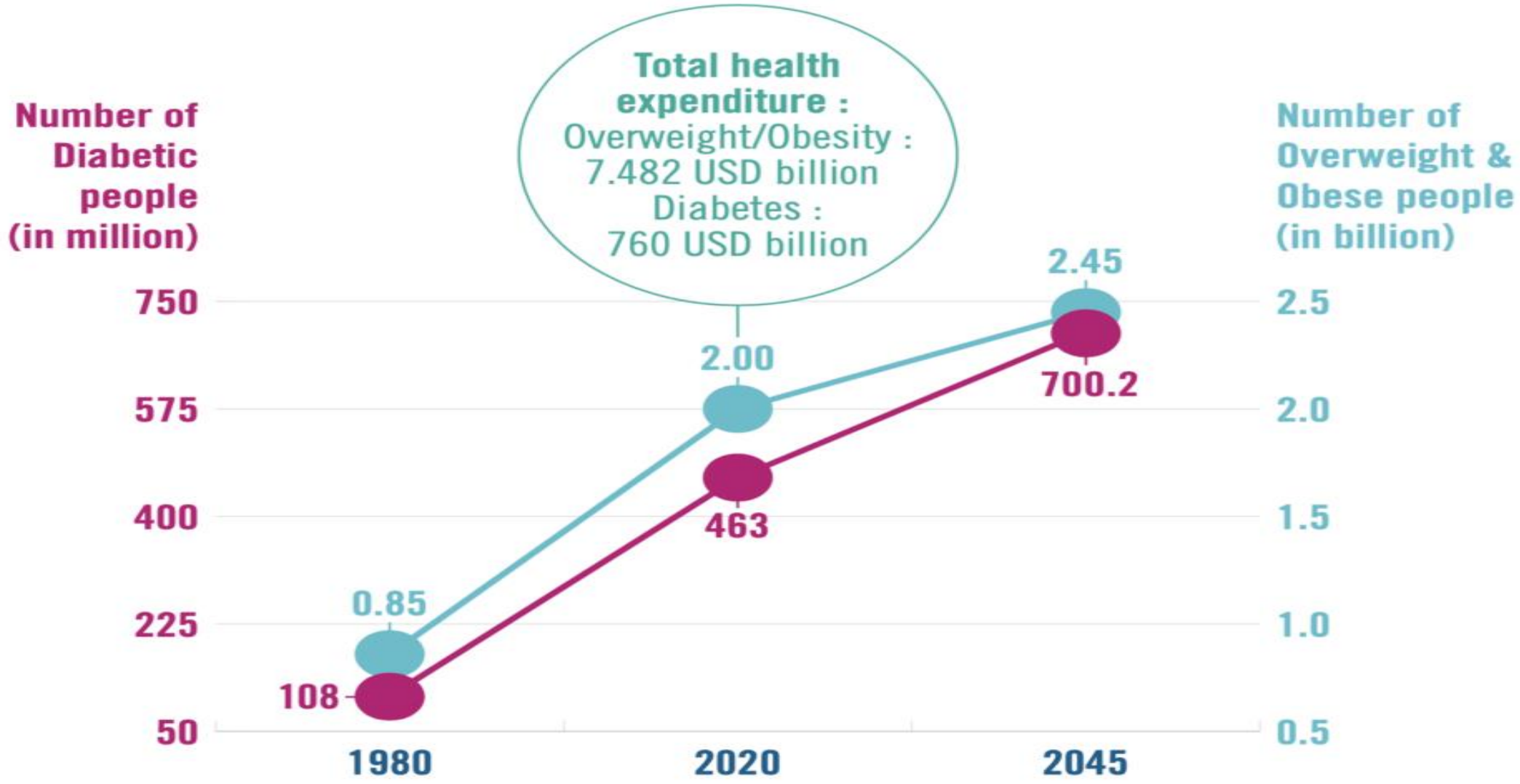
Puri and Sanyal
Clinical Liver Disease, Vol. 1, No. 4, August 2012

Risk Factors Associated With NAFLD

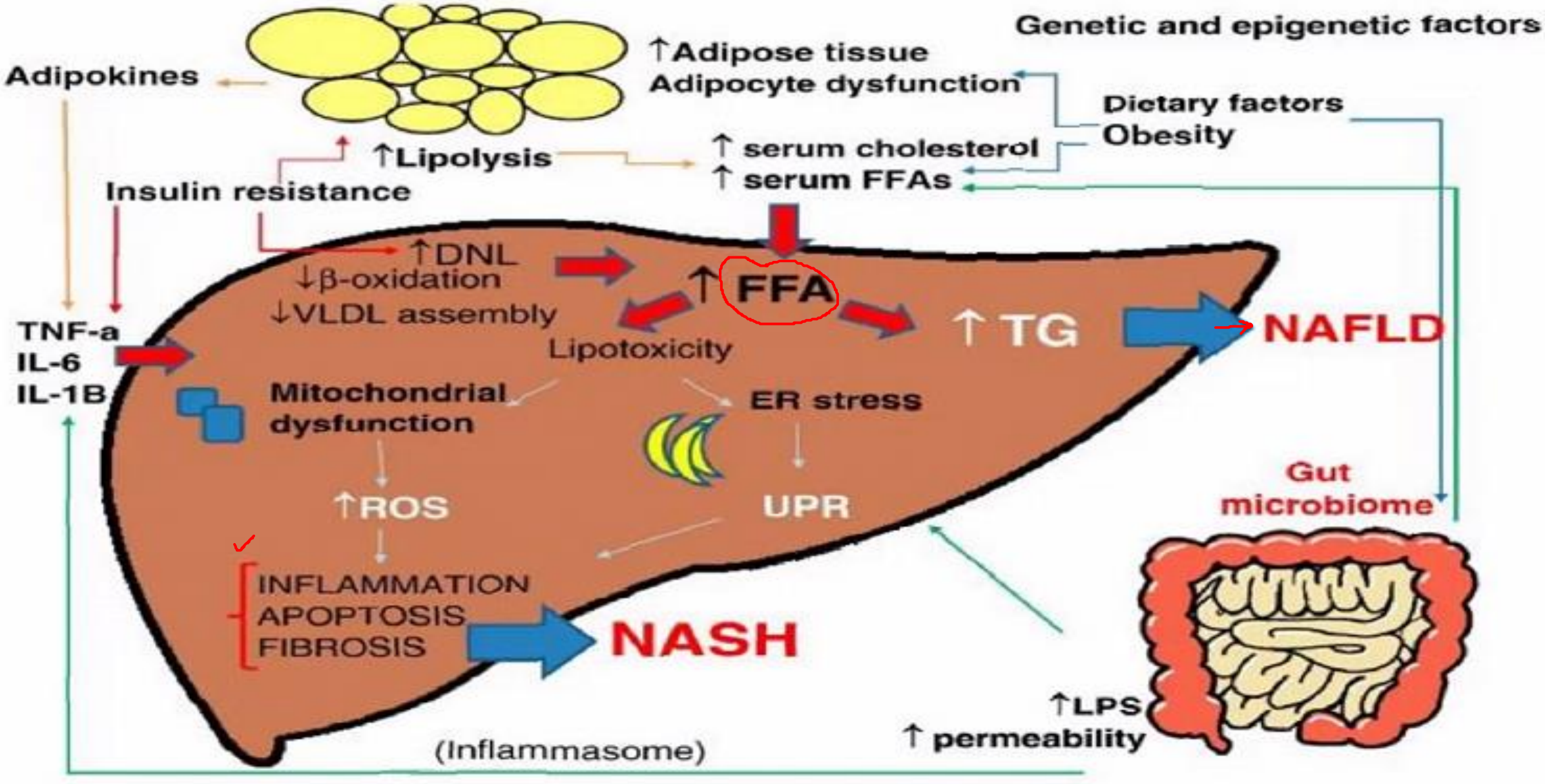
Common Condition with Established Association	*Other Condition Associated with NAFLD*
Obesity	Hypothyroidism
Type 2 DM	Obstructive Sleep Apnea
Dyslipidemia	Hypopituitarism
Mets	Hypogonadism
Polycystic Ovary Syndrome	Pancreatoduodenal Resection
Drugs	Psoriasis

CHALASANI ET AL. HEPATOLOGY, January 2018

OBESITY GRAPH



NAFLD: Pathogenesis



INVESTIGATIONS of NAFLD

Non-INVASIVE

INVASIVE

Non-invasive:

- Abdominal ultrasound (US)
- Magnetic resonance imaging (MRI
- Transient elastography (TE) using CAP
- ALT, AST, Gamma GT
- Fatty Liver Index (FLI)
- The cytokeratin-18 fragment

USG CRITERIA OF FATTY LIVER

MILD

Minimal diffuse increase in echogenicity

MODERATE

Moderate diffuse increase in echogenicity

Slightly impaired visualization of intrahepatic vessels, diaphragm

SEVERE

Marked increase in echogenicity

Poor penetration of posterior liver

Poor or no visualization of intra-hepatic vessels and diaphragm

Assessment of advanced fibrosis:

Noninvasive:

- NAFLD fibrosis score(NFS),
- Fibrosis 4 calculator,
- AST/ALT ratio index,
- Serum biomarkers (ELF panel),
- Fibrotest,
- Transient elastography(TE),
- Magnetic resonance elastography (MRE)

Kaswala DH, Lai M, Afdhal NH. Fibrosis Assessment in Nonalcoholic Fatty Liver Disease (NAFLD) in 2016. Dig Dis Sci. 2016;61:1356–1364. [PubMed] [Google Scholar]

FIBROSCAN

CAP Score	Steatosis Grade	Amount of Liver with Fatty Change
238 to 260 dB/m	S1	11% to 33%
260 to 290 dB/m	S2	34% to 66%
Higher than 290 dB/m	S3	67% or more

FIBROSCAN

Fibrosis score F0 to F1: No liver scarring or mild liver scarring

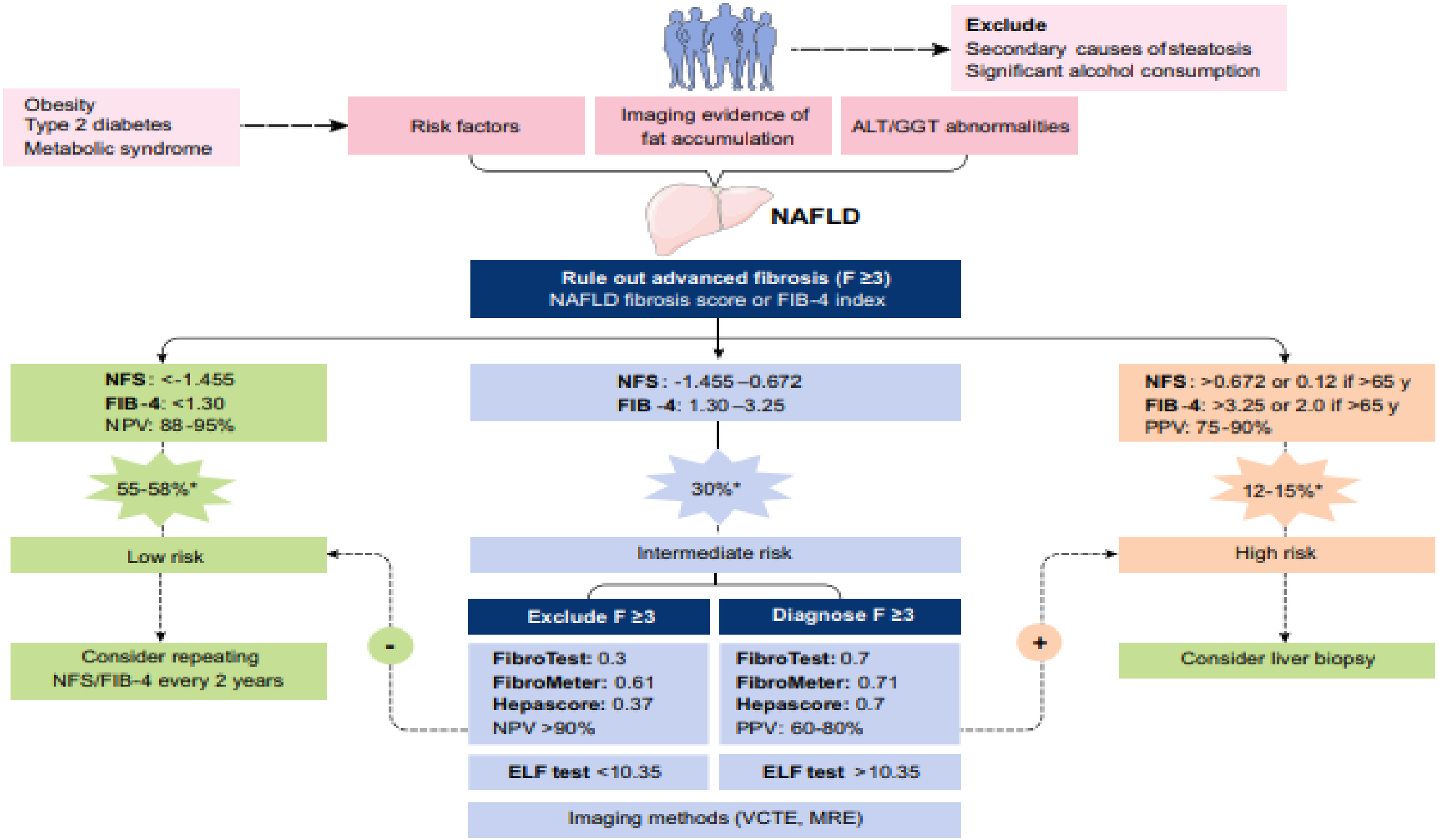
F2: Moderate liver scarring

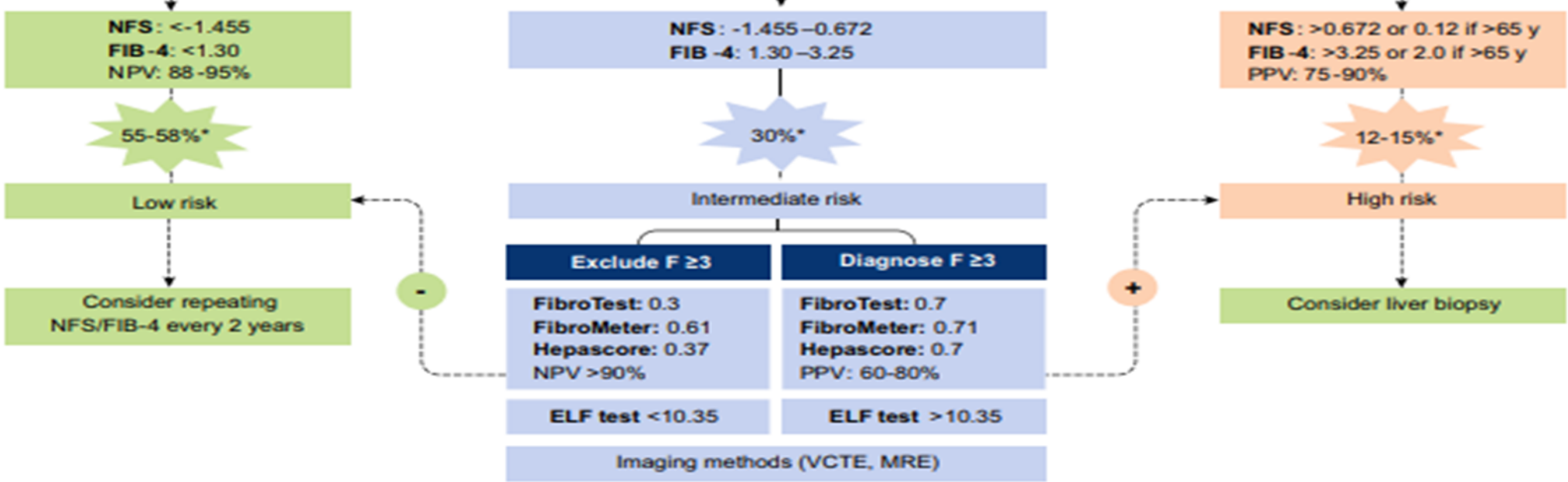
F3: Severe liver scarring

F4: Advanced liver scarring (cirrhosis)

	F0 to F1	F2	F3	F4
NAFLD or NASH	2 to 7 kPa	7.5 to 10 kPa	10 to 14 kPa	>14 kPa

- Algorithm for non-invasive assessment: ***prediction rules*** and blood-based biomarkers




NFS: <-1.455
FIB-4: <1.30
NPV: 88-95%
55-58%*
Low risk
Consider repeating
NFS/FIB-4 every 2 years
-
NFS: -1.455–0.672
FIB-4: 1.30–3.25
30%*
Intermediate risk
Exclude F ≥3
Diagnose F ≥3
FibroTest: 0.3
FibroMeter: 0.61
Hepascore: 0.37
NPV >90%
FibroTest: 0.7
FibroMeter: 0.71
Hepascore: 0.7
PPV: 60-80%
ELF test <10.35
ELF test >10.35
Imaging methods (VCTE, MRE)
+
NFS: >0.672 or 0.12 if >65 y
FIB-4: >3.25 or 2.0 if >65 y
PPV: 75-90%
12-15%*
High risk
Consider liver biopsy

Invasive: Liver biopsy

Who are the candidates?

- **The AASLD guidelines:–**
- in patients with MS
- When NFS, FIB-4 or liver stiffness measured by TE or MRE suggest the presence of advanced liver fibrosis.

- Again, it should be reserved for the following two situations:
  - (1) Uncertain diagnosis;
  - (2) Suspect of NAFLD-related advanced liver disease.

Treatment

3D:

Diet
Discipline
Drug

Components of a lifestyle approach to NAFLD

Energy restriction
Calorie restriction
(500–1,000/day)

Avoid fructose-containing food and drink

Low-to-moderate fat
Low-carbohydrate ketogenic diets or high protein

Coffee consumption

- No liver-related limitations

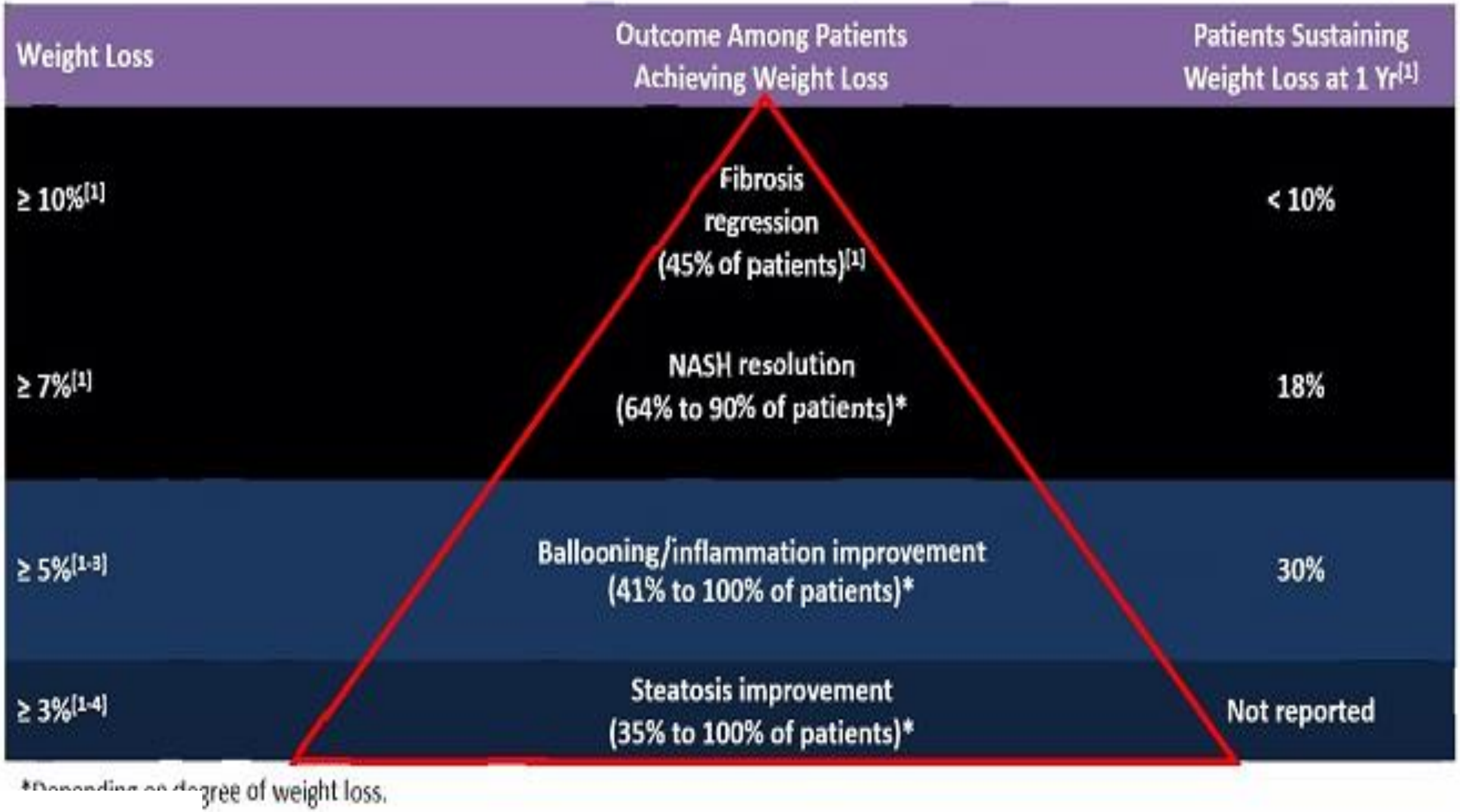
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Activities to Achieve 2008 Exercise Guideline Recommendations

Moderate-Intensity Aerobic Activities >150 min/week	Vigorous-Intensity Aerobic Activities >75 min/week
Brisk walking (>3 miles/h)	Uphill walking or race walking
Bicycling (<10 miles/h)	Bicycling (>10 miles/h)
Water aerobics	Running or jogging
Tennis (doubles)	Tennis (singles)
Ballroom dancing	Aerobic dancing
General gardening	Heavy gardening (digging/hoeing)

From the Centers for Disease Control and Prevention guidelines (12).

Eijsvogels, Thijs & Molossi, Silvana & Lee, Duck-chul & Emery, Michael & Thompson, Paul. (2016). Exercise at the ExtremesThe Amount of Exercise to Reduce Cardiovascular Events. Journal of the American College of Cardiology. 67. 316-329. 10.1016/j.jacc.2015.11.034.



*Depending on degree of weight loss.

NAFLD: Pharmacotherapy

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necro-inflammatory activity

- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH-defining lesions accepted as surrogate endpoint.

*Age > 50 years, diabetes, MetS, increased ALT

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Pharmacological Treatment In NAFLD

- No drugs are approved by USFDA for NAFLD/ NASH
- Medications those are using (based on RCT):
  - Metformin
  - Vitamin E
  - Omega-3 Fatty Acid
  - Statins
  - Ursodeoxycholic acid
  - Empagliflozin
  - *Obeticholic acid*
  - *Pioglitazone*
  - *Liraglutide, semaglutide*
  - *Saroglitazar*

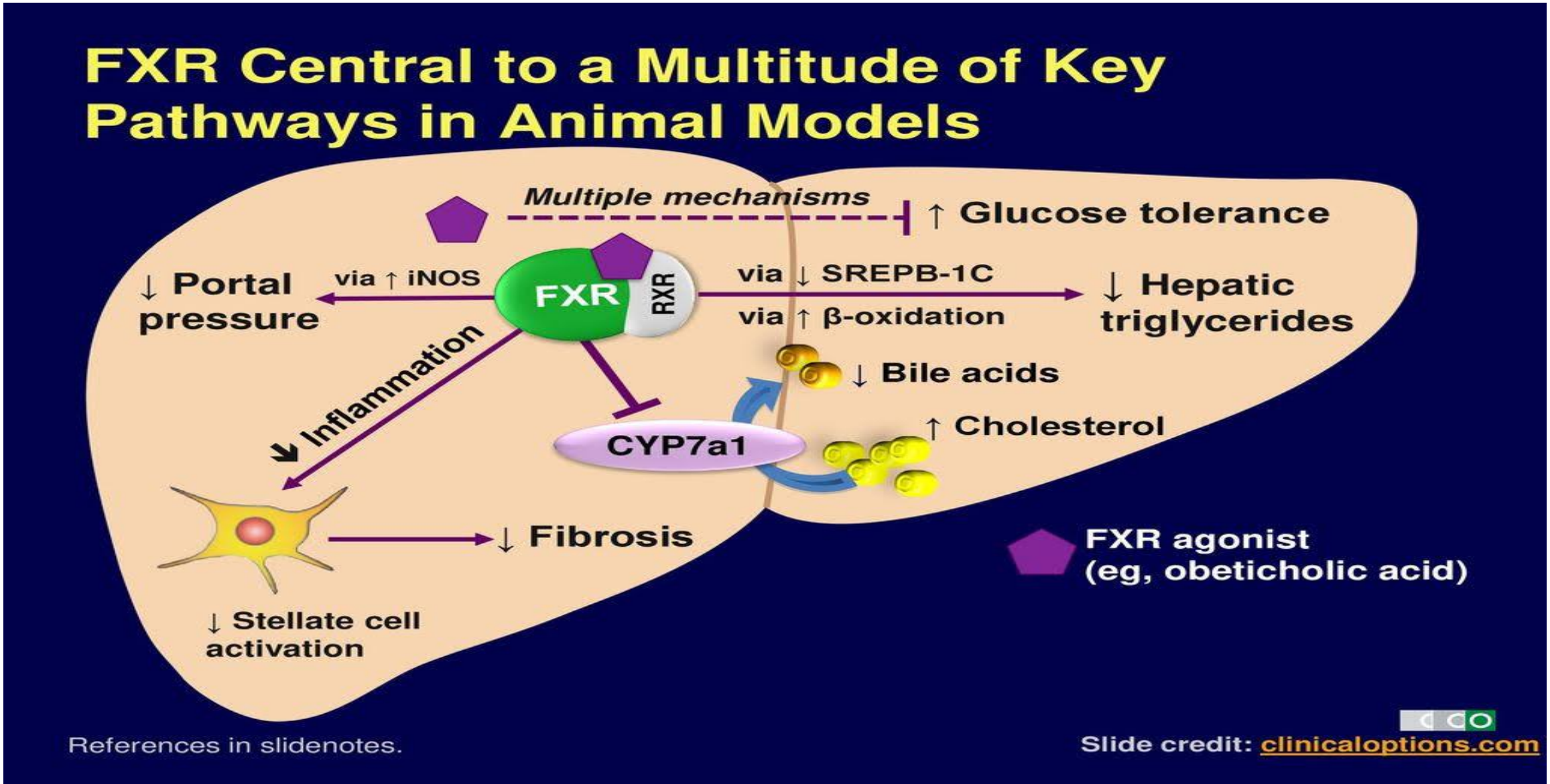
Treatment: pharmacotherapy

- **Insulin sensitizers**
  - **Little evidence of histological efficacy with metformin**

- **Antioxidants**
  - Vitamin-E may improve steatosis, inflammation & ballooning and resolve NASH in some patients
    - Concerns about long-term safety exist

*Most efficacy data, but off-label outside T2DM; †Better safety and tolerability than pioglitazone in the short-term;
‡No recommendations can be made in patients with normal baseline ALT
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

New Hope: Obeticholic Acid (OCA)

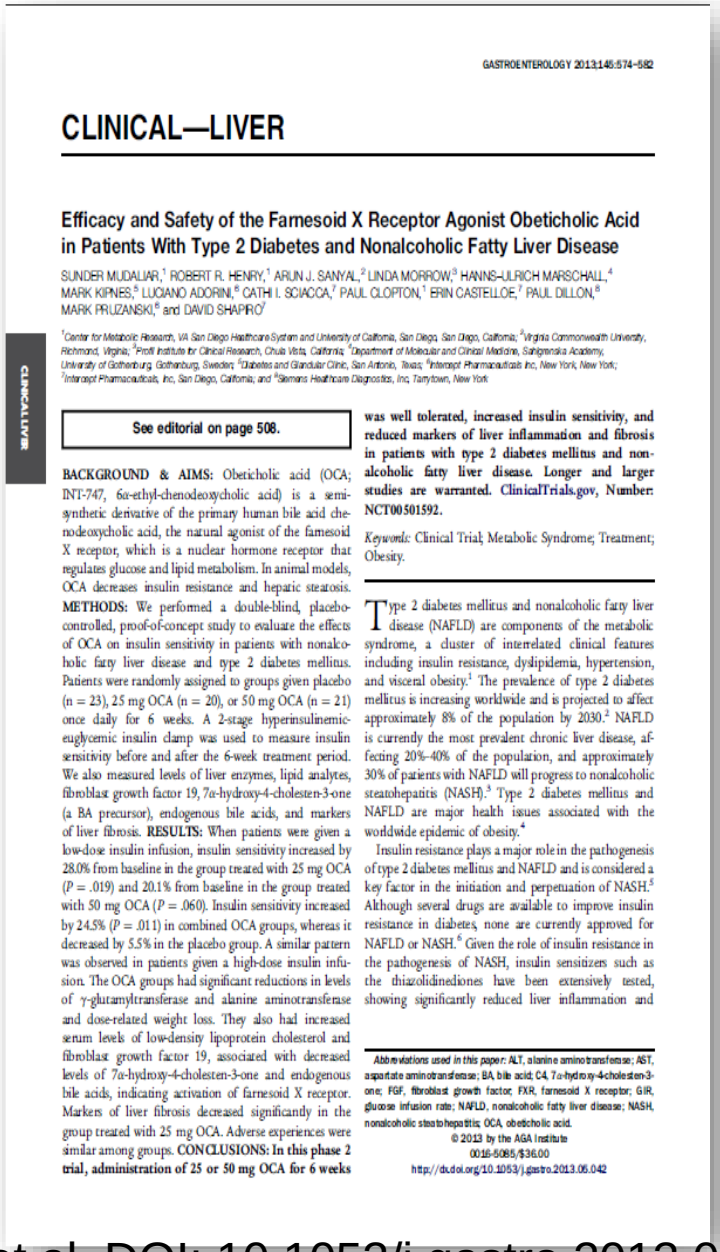


Obeticholic acid in Patients with T2DM and NAFLD

aga American Gastroenterological Association

Efficacy and Safety of the Farnesoid X Receptor Agonist Obeticholic Acid in Patients with Type 2 Diabetes and Nonalcoholic Fatty Liver Disease.

A double-blind, placebo controlled, proof-of-concept study



GASTROENTEROLOGY 2013;145:574–582

CLINICAL—LIVER

Efficacy and Safety of the Farnesoid X Receptor Agonist Obeticholic Acid in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease

SUNDER MUDALIAR,[1] ROBERT R. HENRY,[1] ARUN J. SANYAL,[2] LINDA MORROW,[3] HANNS-ULRICH MARSCHALL,[4] MARK KIPNES,[5] LUCIANO ADORINI,[6] CATHI I. SCIACCA,[7] PAUL CLOPTON,[1] ERIN CASTELLOE,[7] PAUL DILLON,[8] MARK PRUZANSKI,[8] and DAVID SHAPIRO[7]

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See editorial on page 508.

BACKGROUND & AIMS: Obeticholic acid (OCA; INT-747, 6α-ethyl-chenodeoxycholic acid) is a semisynthetic derivative of the primary human bile acid chenodeoxycholic acid, the natural agonist of the farnesoid X receptor, which is a nuclear hormone receptor that regulates glucose and lipid metabolism. In animal models, OCA decreases insulin resistance and hepatic steatosis. **METHODS:** We performed a double-blind, placebo-controlled, proof-of-concept study to evaluate the effects of OCA on insulin sensitivity in patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus. Patients were randomly assigned to groups given placebo (n = 23), 25 mg OCA (n = 20), or 50 mg OCA (n = 21) once daily for 6 weeks. A 2-stage hyperinsulinemic-euglycemic insulin clamp was used to measure insulin sensitivity before and after the 6-week treatment period. We also measured levels of liver enzymes, lipid analytes, fibroblast growth factor 19, 7α-hydroxy-4-cholesten-3-one (a BA precursor), endogenous bile acids, and markers of liver fibrosis. **RESULTS:** When patients were given a low-dose insulin infusion, insulin sensitivity increased by 28.0% from baseline in the group treated with 25 mg OCA ($P = .019$) and 20.1% from baseline in the group treated with 50 mg OCA ($P = .060$). Insulin sensitivity increased by 24.5% ($P = .011$) in combined OCA groups, whereas it decreased by 5.5% in the placebo group. A similar pattern was observed in patients given a high-dose insulin infusion. The OCA groups had significant reductions in levels of γ-glutamyltransferase and alanine aminotransferase and dose-related weight loss. They also had increased serum levels of low-density lipoprotein cholesterol and fibroblast growth factor 19, associated with decreased levels of 7α-hydroxy-4-cholesten-3-one and endogenous bile acids, indicating activation of farnesoid X receptor. Markers of liver fibrosis decreased significantly in the group treated with 25 mg OCA. Adverse experiences were similar among groups. **CONCLUSIONS: In this phase 2 trial, administration of 25 or 50 mg OCA for 6 weeks was well tolerated, increased insulin sensitivity, and reduced markers of liver inflammation and fibrosis in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Longer and larger studies are warranted. ClinicalTrials.gov, Number: NCT00501592.**

Keywords: Clinical Trial; Metabolic Syndrome; Treatment; Obesity.

Type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD) are components of the metabolic syndrome, a cluster of interrelated clinical features including insulin resistance, dyslipidemia, hypertension, and visceral obesity.[1] The prevalence of type 2 diabetes mellitus is increasing worldwide and is projected to affect approximately 8% of the population by 2030.[2] NAFLD is currently the most prevalent chronic liver disease, affecting 20%–40% of the population, and approximately 30% of patients with NAFLD will progress to nonalcoholic steatohepatitis (NASH).[3] Type 2 diabetes mellitus and NAFLD are major health issues associated with the worldwide epidemic of obesity.[4]

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes mellitus and NAFLD and is considered a key factor in the initiation and perpetuation of NASH.[5] Although several drugs are available to improve insulin resistance in diabetes, none are currently approved for NAFLD or NASH.[6] Given the role of insulin resistance in the pathogenesis of NASH, insulin sensitizers such as the thiazolidinediones have been extensively tested, showing significantly reduced liver inflammation and

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; C4, 7α-hydroxy-4-cholesten-3-one; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GIR, glucose infusion rate; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.05.042

Mudaliar et al, DOI: 10.1053/j.gastro.2013.05.042

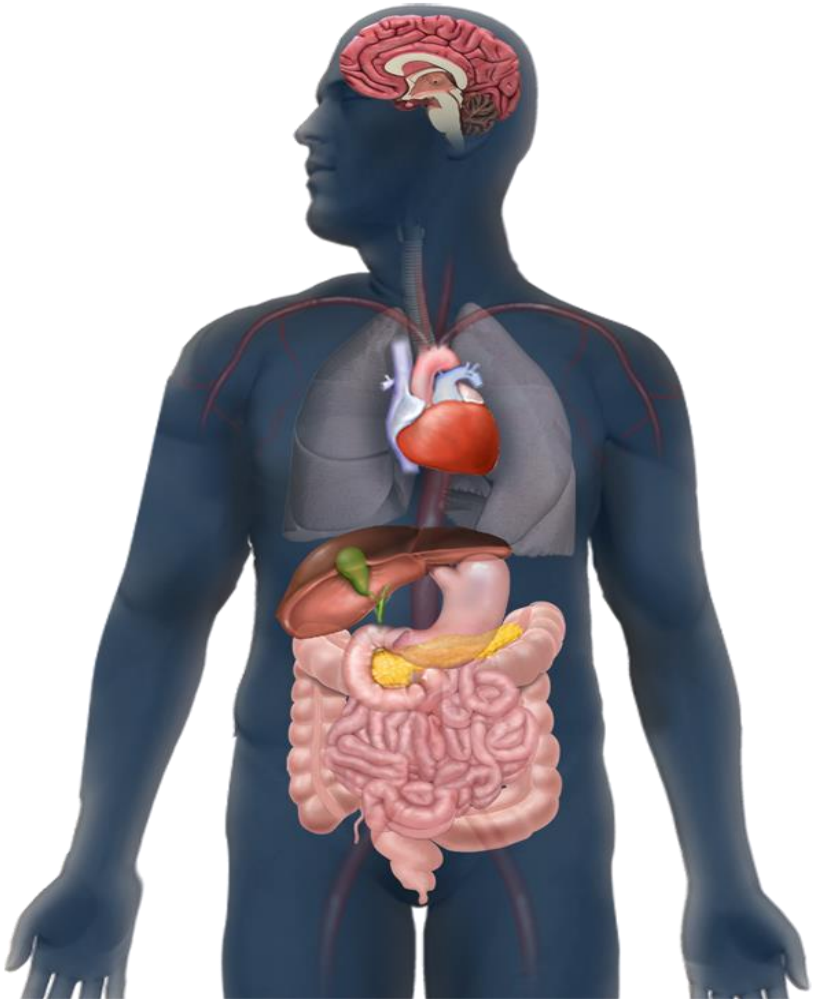
INCRETIN AND GLP-1 ANALOGUE

- GLP-and GIP are incretins
- Secretion of insulin by beta cell by oral carbohydrate intake rather I.V glucose.
- The incretin effect is responsible for 50-70% of total insulin secretion after glucose ingestion
- Incretin effect GLP-1, not GIP, is often reduced in patients with (T2DM)
- Best example:Semaglutide,

Semaglutide effects on Glucose and energy metabolism

Glucose metabolism[1]

- ↑ Insulin secretion (glucose-dependent)
- ↓ Glucagon secretion (glucose-dependent)



Weight reduction [2]

- ↑ Satiety, fullness
- ↑ Control of eating
- ↓ Energy intake
- ↓ Hunger and food cravings

1. Kapitza C et al. *Diabetologia* 2017;60:1390–9; 2. Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51

Take away points- Semaglutide

Consistent glycaemic improvements across the SUSTAIN programme[1–10]

significant weight loss across the SUSTAIN programme[1–10]

well tolerated, with a safety profile typical of GLP-1RAs. Most frequent AEs with semaglutide were GI[1–10]

statistically significant glycaemic control and weight reduction

Weight loss and improvement of DM-may be beneficial for Mx of fatty liver and NASH

Three-component MACE included CV death, non-fatal MI, and non-fatal stroke.
AE, adverse event; CV, cardiovascular; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MI, myocardial infarction.
1. Sorli C et al. *Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén B et al. *Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258–66; 4. Aroda VR et al. *Lancet Diabetes Endocrinol* 2017;5:355–66; 5. Rodbard HW et al. *J Clin Endocrinol Metab* 2018;103:2291–301; 6. Marso SP et al. *N Engl J Med* 2016;375:1834–44; 7. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86; 8. Lingvay I et al. *Lancet Diabetes Endocrinol* 2019;7:834–44; 9. Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7:356–67; 10. Capehorn MS et al. *Diabetes Metab* 2020;46:100–9.

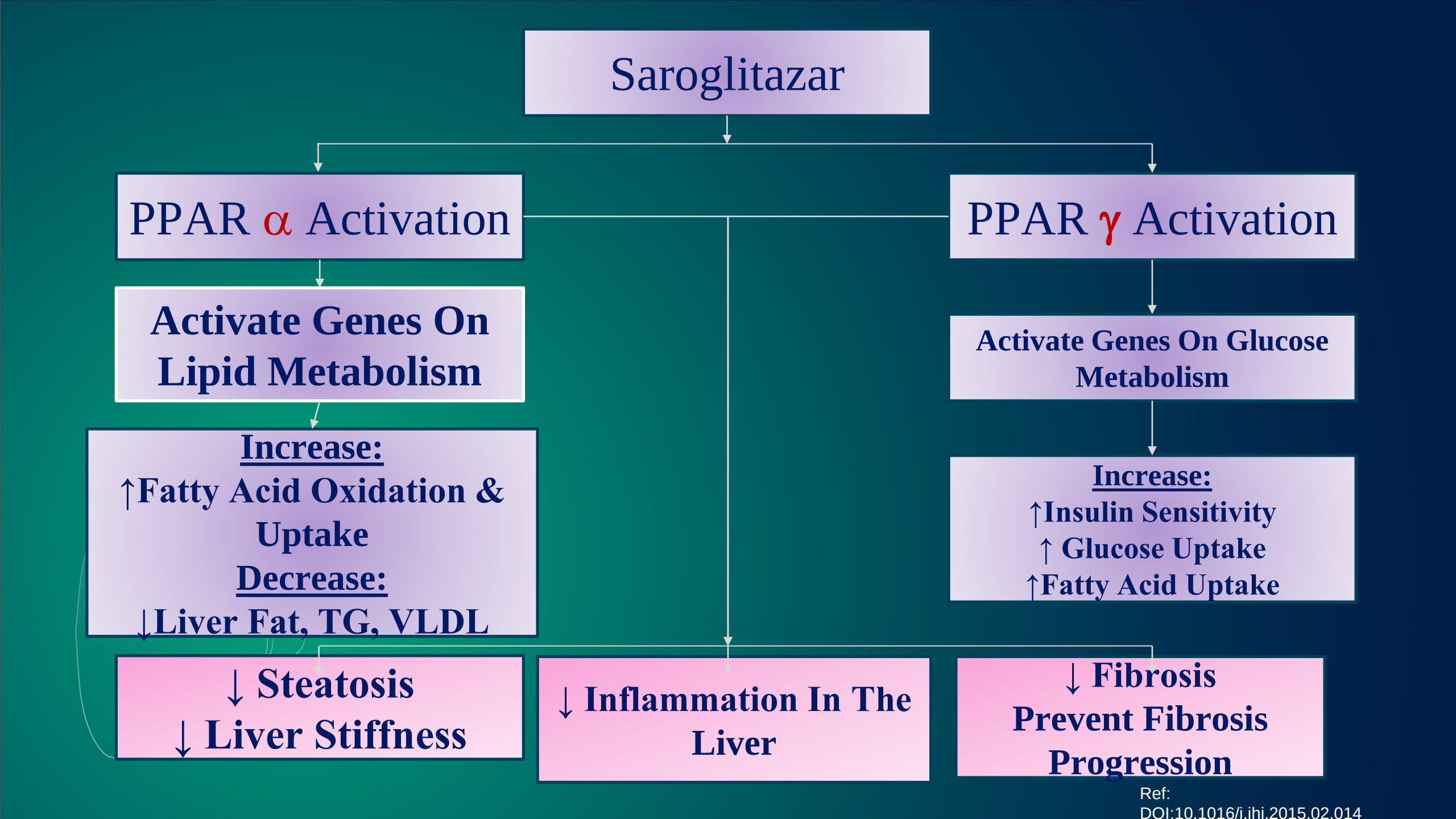
- **Peroxisomal Proliferator-Activated Receptors (PPAR):**
  - **Pioglitezone**
  - **Saroglitazar**

Inflammation

- **Alpha**
  - Down-regulates IL-1, IL-6, CRP in the liver
  - Upregulates catalase

- **Gamma**
  - Induces M2 macrophage polarization (Anti-inflammatory)

- **Delta**
  - Reduces expression of pro-inflammatory genes TNF alpha, IL-1B



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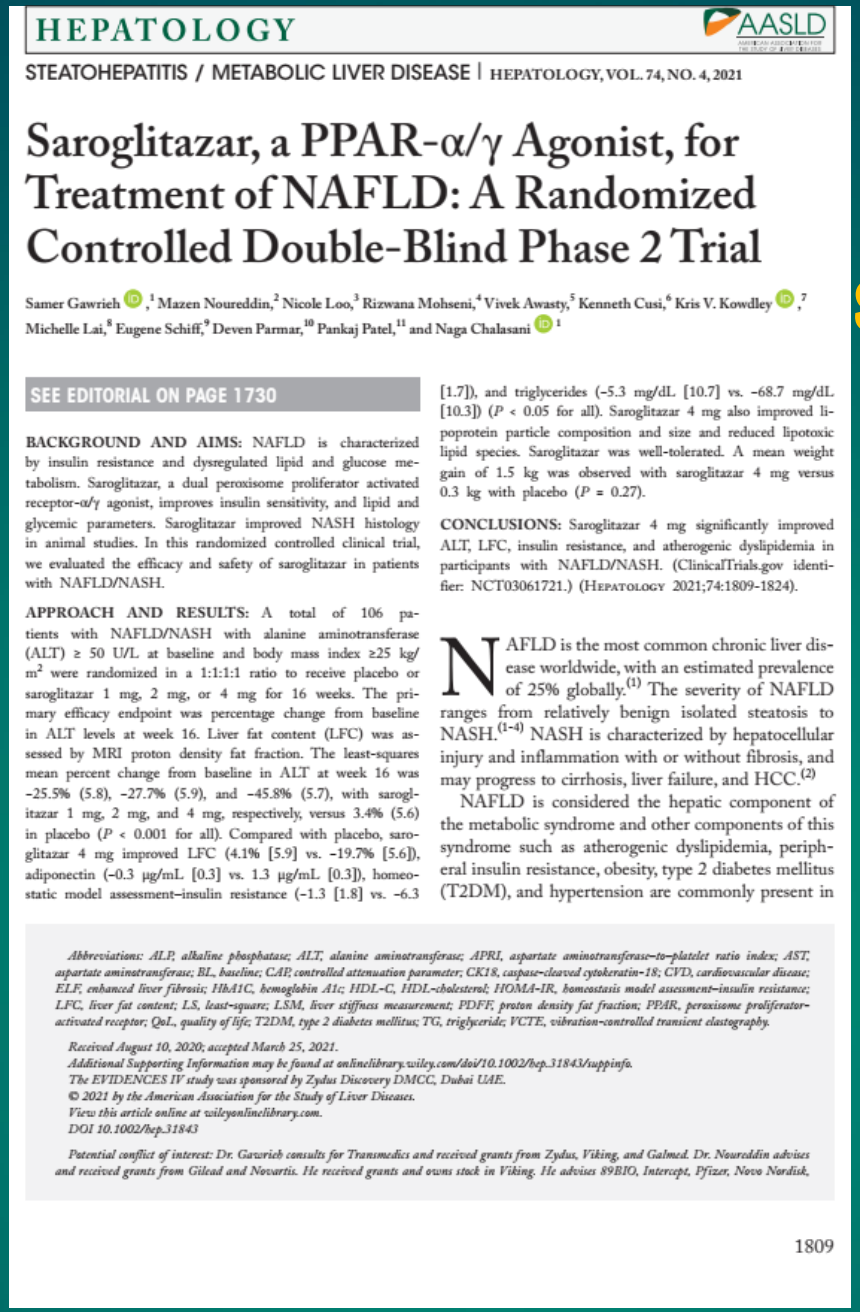
DOI:10.1016/j.jhj.2015.02.014



HEPATOLOGY

AASLD

STEATOHEPATITIS / METABOLIC LIVER DISEASE | HEPATOLOGY, VOL. 74, NO. 4, 2021

Saroglitazar, a PPAR-α/γ Agonist, for Treatment of NAFLD: A Randomized Controlled Double-Blind Phase 2 Trial

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SEE EDITORIAL ON PAGE 1730

BACKGROUND AND AIMS: NAFLD is characterized by insulin resistance and dysregulated lipid and glucose metabolism. Saroglitazar, a dual peroxisome proliferator activated receptor-α/γ agonist, improves insulin sensitivity, and lipid and glycemic parameters. Saroglitazar improved NASH histology in animal studies. In this randomized controlled clinical trial, we evaluated the efficacy and safety of saroglitazar in patients with NAFLD/NASH.

APPROACH AND RESULTS: A total of 106 patients with NAFLD/NASH with alanine aminotransferase (ALT) ≥ 50 U/L at baseline and body mass index ≥25 kg/m^2 were randomized in a 1:1:1:1 ratio to receive placebo or saroglitazar 1 mg, 2 mg, or 4 mg for 16 weeks. The primary efficacy endpoint was percentage change from baseline in ALT levels at week 16. Liver fat content (LFC) was assessed by MRI proton density fat fraction. The least-squares mean percent change from baseline in ALT at week 16 was −25.5% (5.8), −27.7% (5.9), and −45.8% (5.7), with saroglitazar 1 mg, 2 mg, and 4 mg, respectively, versus 3.4% (5.6) in placebo ($P < 0.001$ for all). Compared with placebo, saroglitazar 4 mg improved LFC (4.1% [5.9] vs. −19.7% [5.6]), adiponectin (−0.3 μg/mL [0.3] vs. 1.3 μg/mL [0.3]), homeostatic model assessment–insulin resistance (−1.3 [1.8] vs. −6.3 [1.7]), and triglycerides (−5.3 mg/dL [10.7] vs. −68.7 mg/dL [10.3]) ($P < 0.05$ for all). Saroglitazar 4 mg also improved lipoprotein particle composition and size and reduced lipotoxic lipid species. Saroglitazar was well-tolerated. A mean weight gain of 1.5 kg was observed with saroglitazar 4 mg versus 0.3 kg with placebo ($P = 0.27$).

CONCLUSIONS: Saroglitazar 4 mg significantly improved ALT, LFC, insulin resistance, and atherogenic dyslipidemia in participants with NAFLD/NASH. (ClinicalTrials.gov identifier: NCT03061721.) (HEPATOLOGY 2021;74:1809-1824).

NAFLD is the most common chronic liver disease worldwide, with an estimated prevalence of 25% globally.[1] The severity of NAFLD ranges from relatively benign isolated steatosis to NASH.[1-4] NASH is characterized by hepatocellular injury and inflammation with or without fibrosis, and may progress to cirrhosis, liver failure, and HCC.[2]

NAFLD is considered the hepatic component of the metabolic syndrome and other components of this syndrome such as atherogenic dyslipidemia, peripheral insulin resistance, obesity, type 2 diabetes mellitus (T2DM), and hypertension are commonly present in

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase–to–platelet ratio index; AST, aspartate aminotransferase; BL, baseline; CAP, controlled attenuation parameter; CK18, caspase-cleaved cytokeratin-18; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; HbA1C, hemoglobin A1c; HDL-C, HDL-cholesterol; HOMA-IR, homeostasis model assessment–insulin resistance; LFC, liver fat content; LS, least-square; LSM, liver stiffness measurement; PDFF, proton density fat fraction; PPAR, peroxisome proliferator-activated receptor; QoL, quality of life; T2DM, type 2 diabetes mellitus; TG, triglyceride; VCTE, vibration-controlled transient elastography.

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Saroglitazar, a PPAR-α/γ Agonist, for Treatment of NAFLD: A Randomized Controlled Double-Blind Phase 2 Trial

- **Study Type:** Multicentre, randomized, double-blind, placebo-controlled phase 2 study to evaluate the safety and efficacy of saroglitazar (4 mg) compared with placebo in patients with NAFLD/NASH treated for 16 weeks.
- **Population:** A total of 54 *(Saro 4=26, Placebo=28)* patients with NAFLD/NASH
- **Centre:** Different medical centres in the USA
- **Duration:** June 2017 and August 2019 (ClinicalTrials.gov identifier: NCT03061721)

INASL 2022 Recommendations On Drugs for NAFLD

VITAMIN-E

- At 800 mg IU/Day in 2 divided doses
- Recommended in NASH adults without diabetes only
- Decrease in ALT, improves liver histology but not Fibrosis
- No effect on fibrosis
- No significant change in lipid profile
- **Long-term safety concerns**
  - Increased risk of **Hemorrhagic stroke**
  - Increase the risk of All-Cause **Mortality** >800 IU/day
  - Increased risk of **Prostate Carcinoma** risk
- Suggested duration – 2 years

PIOGLITAZONE

- 30 mg/d, minimum duration 2 years
- Decrease in ALT, improve insulin resistance & steatosis
- Improves biopsy-proven NASH with T2D **(off-label indication)**
- No effect on fibrosis & lipid profile
- Proven to cause **weight gain**
- Cautiously used in Pts with **cardiomyopathy & postmenopausal women**
- **↑ risk of Edema & Congestive heart failure: ↑ CV risk**
- **↑ Bone-loss & fractures in Post-menopausal females**

SAROGLITAZAR

- **NASH with or without hepatic fibrosis** (F1–F3) in **both diabetic and nondiabetic adult patients**
- 4 mg OD, min duration 1 year
- Only approved drug for **NAFLD/NASH by DCGI**
- **Anti-steatosis, Anti-Inflammatory, Anti-Fibrotic**
- **Decrease in ALT & Steatosis**
- **Improve insulin resistance**
- **Decrease in Triglycerides with improved Lipoprotein particle composition**
- **Reduction in fibrosis (NAS)**
- No significant effect on body weight
- **Better efficacy in Diabetic Dyslipidemia with High TG**

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CONCLUSION:

- Fatty liver disease is the most common liver disease worldwide
- Bangladesh is experiencing increasing trend of NAFLD
- Lifestyle changes and treatment comorbid conditions are playing important role.


Thank
you!